REMARKS

Status of Claims

Claims 37-44, 47 and 52-72 are pending in the present application.

Amendments to the Claims

Claims 1-36, 45, 46, and 48-51 are cancelled.

Claims 37, 66 and 69 are amended to remove sonicated *Mycobacterium w* and solvent extract *Mycobacterium w* to overcome objections raised by the Examiner, and to recite that the composition "is selected from the group consisting of" as necessary in Markush practice in the amended claims.

Claim 70 is appropriately amended and the phrase "*administered by intradermally* is changed to "*administered intradermally*".

These amendments and cancellations of claims are made without prejudice.

Applicants also call attention to the co-pending U.S. Patent Application Serial No. 10/565,211 by Bakulesh Khamar (an applicant/inventor in this application) of common assignment with this application. In the '211 application claim 48 was allowed, claims 49-54 appear to be allowable and claims 22-29, 32, 34, 36-43 and 45-47 are rejected. Prosecution is and will be continuing therein.

Addressing now the rejection herein on lack-of-enablement, the enclosed Rule 132 Declaration of one of the inventors of the present invention (a well qualified declarant) shows the following responses to concerns and questions expression by the Examiner in the February 18, 2010 Office Action.

a. The declaration states that the actual composition used in the specification examples demonstrating medical effect (as in Examples 4 to 9), was the one provided in Example 1a which consists of 0.5×10^9 heat killed whole cells of *Mycobacterium w* in 0.1 ml. But the other disclosed compositions are also usable.

b. He further states that the dose administered was:

- 0.1 ml as per example 4 to 8
- 0.2 ml initial dose as per example 8b, paragraph [0108]
- 0.3 ml as per Example 9

c. The route of administration in all examples of administration was intradermal, through intramuscular is also disclosed separately.

d. The frequency of administration was:

Once a month
Example 5 of paragraph [0093], line 4,
Example 6 of paragraph [0097], line 4

Once every two weeks
Example 8(a) of paragraph [0105], line 7
Example – 8(b) of paragraph [0108], line 6-8

Once a week
Example 8(a) of paragraph [0105], line 6
Example 4, Case 1, para [0085], line 9 and case 3, para [0089], line 11.

Biweekly
Example 9 of paragraph [0113], line 6

e. Regarding support for enablement as to muscle invasive bladder cancer, it was shown in the declaration that:

i. As to muscle invasive bladder cancer – Para [0099] of the application states that

'Thus *Mycobacterium w* is effective in achieving complete remission and maintaining it'.

Complete remission is also called complete response and it means the disappearance of all signs of cancer in response to treatment. This is the professional understanding of complete remission.

The declaration cited: National Cancer Institute's Dictionary of Cancer Terms. Available: "Complete Remission." (Access date August 9, 2010, Link: **http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=45651**) and a copy is filed herewith.

Thus, the present invention provided complete response to therapy and not just to reduced bladder lesions as indicated by the Examiner (Page No. 7, line 30, of the Office Action).

f. Responding to the Examiner's question as to the effect of the *Mycobacterium w* composition in view of radio therapy, the declaration draws attention to the following facts:

i. 'Local control rates with radiation alone for muscle invading tumors have been disappointingly low and radiation as mono therapy has largely been abandoned. (See Kaufman et al Annal of Oncology 2006, 17 (Supplement 5) v.106-v112 and a copy is filed herewith.

ii. Various modalities have been tried at least since 1985 to improve outcomes of bladder pressuring approach for muscle invasive bladder cancer. The approaches include trans urethral bladder resection (TURBT) with radiotherapy and /or chemotherapy. The declaration cited William [Shipley] et al, Cancer Suppl, April 15, 2003 Vol. 97, No. 8, 2115-2119 and a copy is filed herewith.

iii. Example 6 illustrates complete remission of muscle invasive bladder cancer using *Mycobacterium w* and radiotherapy in absence of TURBT in all cases (100% complete response). All remained disease free till the end of follow-up.

None of the subjects noticed any side effect of radiotherapy and/or *Mycobacterium w*.

Thus Example 6 illustrates effect of *Mycobacterium w* in achieving complete remission and maintaining it. It also illustrates lack of side effects of *Mycobacterium w* as well as radiotherapy.

g. The declaration shows that currently, there is no systemic therapy for treatment of superficial bladder cancer. Currently superficial bladder cancer is treated by TURBT followed by intravasical BCG and / or chemotherapy. Example 5 illustrates efficacy of *Mycobacterium w* in absence of TURBT and intravasical therapy.

h. Regarding efficacy of *Mycobacterium w* in refractory cancer as a stand alone therapy, the declaration noted that treatment by the present invention of cancer refractory to

standard therapy, as in the specification cases 1 and case 3, illustrates efficacy of *Mycobacterium w* in refractory cancer as a stand alone therapy.

i. The declaration shows that the present specification teaches fully on how to enable making of and using the present invention. As to making, the production of the pharmaceutical compositions including *Mycobacterium* w are well described. As for using, the specification relies on well known per se methods of dose selection and administration protocols and adapting those to particular circumstances can be done without undue experimentation.

j. The declaration also shows at section 13 that Cadila, the assignee of the present application, is conducting four phase one clinical trials under supervision of U.S. and India health authorities.

(a) Study NCT 00694798 (USFDA): "Study of *Mycobacterium w* in BCG Refractory Superficial Transitional Cell Carcinoma of Bladder (STCC)."

The protocol admits patients who have failed to achieve disease-free state at six months after initiation of therapy or patients who have recurrence of tumor within three months after completion of treatment or adequate retreatment, but excluding patients with certain co-morbidity conditions, including i.e., immuno-compromised.

(b) Study NCT00525408 (US FDA): "A Study of Mycobacterium w Plus Docetaxel for Hormone Refractory Metastatic Prostate Cancer (HRPC)"

The protocol admits patients with prostate cancer who have become refractory to hormone therapy and also has developed metastasis. This is a controlled trial wherein efficacy of Mycobacterium w plus Docetaxel is compared with Docetaxel alone (Standard of Care).

(c) Study NCT00694915 (US FDA): "Study of Mycobacterium w in Superficial Transitional Cell Carcinoma of Bladder (STCC)"

The protocol admits patients with newly diagnosed superficial transitional cell carcinoma with completely resected papillary tumors and high probability of recurrence risk i.e. stage T1 Grade 2, T1 Grade 3 & CIS. This is a controlled study to compare efficacy of Mycobacterium w intradermal to intravesical BCG (Standard of care) in patients with superficial bladder cancer.

(d) Study NCT00680940 (US FDA): A Study of Mycobacterium w in Combination With Paclitaxel Plus Cisplatin in Advanced Non Small Cell Lung Cancer (NSCLC)

The protocol admits patients with advanced small cell lung cancer. This is a controlled study to compare efficacy of Mycobacterium w in combination with Paclitaxel plus Cisplatin in advanced non small cell lung cancer to that of Paclitaxel plus Cisplatin (Standard of Care).

The above investigations are at several prominent hospitals in India. The investigators have no difficulty, to the best of the declarant's information and belief, in using the present invention. The health regulatory authorities who approved the trials had no difficulty, to the best of his information and belief, in understanding how to use the invention.

Further, the following five abstracts of articles by investigators using *Mycobacterium* w per the present invention, accepted by the American Society for Clinical Oncology ("ASCO") show efficacy and safety of the present invention.

ABSTRACT 1

Improvement in quality of life and symptom control with MYCOBACTERIUM W (CADI-05) in head and neck cancer.

Sub-category:
Immunobiology
Category:
Tumor Biology and Human Genetics
Meeting:
2007 ASCO Annual Meeting
Abstract No:
21186
Citation:
Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 21186
Author(s):
R. I. Dave, U. B. Tripathi, B. J. Parikh, K. M. Patel, H. K. Shukla

Abstract:

Background: Recurrent, radiated and chemotherapy given patients are having many unmanageable symptoms and problems. This condition is worsened by malnutrion, infection, pain and immuno suppression. Modifying immune mechanism of the body is the last and best weapon to fight against such diseases. Role of immunotherapy in the treatment of malignant diseases is on experimental level. Dr George Thyphrontis & Michael Kousilers have produced good results in carcinoma of urinary bladder, melanoma & lung cancer with Immunotherapy. At GCRI, we have tried vaccine, prepared from mycobacterium-W in 100 cases of Head & Neck Cancer.

Methods: As a prospective nonrandomized study, to see beneficiary effect on quality of life and symptom control, we have done a trial during Jan. 2004 to Dec.2005. Informed consent and ethical clearance was obtained. Study was made to find out any side effect or adverse reactions of the vaccine. After fulfilling the criteria of inclusion and exclusion the case was selected for study and 0.1 ml vaccine (CADI-05) was injected intradermally with all aseptic precautions.
Four injections, weekly and later on four injections monthly were given. Patient was followed up for 6 months.

Results: Total No. of cases -100. M / F - 89/11. age distribution - Maximum No. were in 5^{th} decade -(34%) followed by 6^{th} decade (21%)Site of primary - Commonest site was Buccal mucosa (29%) followed by tongue (17%). There was no major side effect. Only 5% Patients developed constitutional symptoms and infection at injection site. 27% patients had pain relief. Symptom control was seen in 15% patients. Improvement in quality of life was observed in 82% of patients. 4% of patients had no effect. The beneficiary effect lasted for three month in 27% patients and more than six months in 13% patients. The effect was more marked in dysphagia, ulcer and fistula. Effect was insignificant in strider, change in voice and metastatic nodes. Four patients are living with Immuvac in spite of disease symptom free for more than one year.

Conclusions: Immunotherapy with Mycobacteium W can safely be used to improve quality of life and control of symptom in terminally ill Head & Neck cancer.

ABSTRACT 2

Use of Immunomodulater Mycobacterium w vaccine for Palliative Treatment in advanced & incurable cancer patients

Sub-category:
Vaccines
Category:
Developmental Therapeutics: Immunotherapy
Meeting:
2005 ASCO Annual Meeting
Abstract No:
2592
Citation:
Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 2592
Author(s):
R. I. Dave, S. V. Shah, K. M. Patel, U. B. Tripathi, A. S. Kapadia, H. P. Panchal

Abstract:

Background Immuno-therapy for prevention and treatment of malignant disease is in experimental stage. Initial work for urinary bladder cancer, melanoma and lung cancer has raised a hope that improving immune mechanisum can be of use.

Method A prospective study was conducted at Gujarat Cancer & Research Institute from December 2003 to December 2004 to assess effect of tuberculosis vaccine **(Mw)**on tumor size, symptoms, and quality of life in 100 patients of advanced cases of carcinoma. The inclusion criteria were positive biopsy of malignancy, measurable disease, all available established treatment have exhausted, no other proved anti cancer treatment is going on and disease has been confirmed to be incurable by team of oncologist with life expectancy more than two months. Intradermal 0.1ml Mw was administered once a week for 5 weeks. Patients were evaluated every week for effect on tumor, symptoms and quality of life. Patients were followed up for 2 months.

Result 77 cases had complete follow up. Male/Female ratio was 44/33. Commonest site of primary was Head and Neck Tumors and histology was squamous cell carcinoma. Out of 77 patients, 27-showed partial response associated with symptomatic improvement. Pain relief and reduction in opioid analgesic requirement was also noted. It was significant in 21 cases. In 4 patients, with non-healing sinus and Fistula, healing was observed. Relief of dysphagia found in 2 cases. There was no systemic side effect seen. There was improvement in quality of life in all patients.

Conclusion In terminally ill advanced cancer patient use of intradermal Mw is useful for tumor regression, improved clinical response. Mw was not associated with any untoward side effects.

ABSTRACT 3

Role of Mycobacterium W as an adjuvant treatment of Head & Neck Cancer--A Randomised trial

Sub-category:
Head and Neck Cancer
Category:
Head and Neck Cancer
Meeting:
2005 ASCO Annual Meeting
Abstract No:
5588
Citation:
Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 5588
Author(s):
S. K. Sarkar, C. Dasgupta

Abstract:

Background: In India,Head & Neck cancer is the commonest malignancy in males.In advanced stage, acute toxicites related to treatment(by radiotherapy and/or chemotherapy) give rise to severe compliance problems. In an effort to reduce treatment-induced toxicity with resultant improvement in quality of life, we used an active non-specific immunomodulator Mycobacterium W, which stimulates the immune system without targetting specific tumour associated antigens .

Methods: 30 patients with histologically proved squamous cell carcinoma of Head & Neck & NO prior exposure to radiotherapy/chemotherapy/immunotherapy with good performance status(<2 in ECOG scale) irrespective of stage & normal CBC/LFT/KFT were included in the study.Mandatory informed consent was taken from each patient. 0.1 ml of Mycobacterium W was given intra-cutaneously weekly during radiotherapy(6000-6600 cGy/6-6½ weeks) along with Cisplatin 30 mg/m² weekly for 6 weeks. Intra-cutaneous injection of Mycobacterium W was continued every 2 weeks for another 3 months after completion of radiation schedule. 30 evenly matched Head & Neck cancer patients were included in the control arm and treated by the same schedule but without any adjuvant immunomodulator. All the patients were examined in detail at monthly intervals.

Results: No grade III skin or hematological toxicity was observed in the study arm & all 30 patients in the study arm completed the treatment protocol without interruption,whereas,12 out of 30 patients in the control arm developed grade III skin/mucous membrane/hematological toxicities leading to interruption of treatment schedule & much prolonged treatment time. As regards disease response, there is no statistically significant difference between the 2 treatment arms. Quality of life as measured by Karnofsky Performance Status is SIGNIFICANTLY better in the study arm.

Conclusions: In a developing country like India, Mycobacterium w is an economically viable & well tolerated immunomodulator for Head & Neck Cancer patients, producing significant reduction in treatment related acute toxicities & leading to enhanced radiation tolerance. Moreover performance statues and quality of life are significantly improved.

ABSTRACT 4

Poly TLR agonist polyantigenic vaccine (Mycobacterium w) in palliative therapy of head and neck cancer.

Print this page

Sub-category:
Vaccines
Category:
Developmental Therapeutics: Immunotherapy
Meeting:
2006 ASCO Annual Meeting
Abstract No:
12512
*Citation:
Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 12512
Author(s):
R. I. Dave, U. Tripathi, S. Shah, K. M. Patel
Abstract:

Background: Poly TLR poly-antigenic vaccine containing Mycobacterium w (Mw) is found useful in the management of lung cancer and bladder cancer when used along with standard therapy[1,2] but not in Head and Neck cancer[3-4]. This study was carried out to evaluate its efficacy as a single agent in advanced head & neck cancer.

Methods: In a prospective study consecutive 75 symptomatic patients with advanced head & neck cancer (squamous cell) attending hospital for palliative care following failure of standard therapy were administered Mw once a week for 8 weeks.

Results: Of 75 patients 43 were male & 32 females with 76% between the ages of 31 to 60). 18 had buccal mucosa tumor, 12 alveolar and 11 at base of the tongue. Partial response was seen in 27. It was associated with Pain relief (27/27), Healing of ulcer/fistula (4/5), improvement in dysphagia (7/15), improvement in voice(5/19). All 27 showed improvement in constitutional symptoms also. No systemic side effects were seen.

Conclusions: Mw vaccine is useful in palliative care of head & neck cancer.

ABSTRACT 5

Role of immuno-therapy as a adjuvant treatment in advance head & neck cancer, patient receiving chemo radiotherapy.

Sub-category:
Vaccines
Category:
Developmental Therapeutics: Immunotherapy
Meeting:
2005 ASCO Annual Meeting

Abstract No:
2598
Citation:
Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 2598
Author(s):
M. C. Pant, R. Hadi, R. Prasad, D. Dalela, R. Pant, D. Parmar, M. Srivastava, S. Parikh
Abstract:

Background In India, Head & Neck cancer is the commonest malignancy in males and gradually on rise. Immuno-therapy for prevention and treatment of malignant disease is in experimental stage. So we used tuberculosis vaccine containing Mycobacterium w for management of advance cancer as a adjuvant therapy.

Method In a randomized controlled study was conducted at King George's Medical University & LCI to evaluate effect of vaccine containing Mw in Head & Neck cancer patients, receiving chemo Radiotherapy (60-70Gy with cisplatin 50 mg weekly for 6-7 weeks). Vaccine was given 0.1 ml Intradermally on weekly basis for 6 to 10 weeks. Patients were followed up for effect of therapy on tumor progression, side effect profile and Karnofsky performance Scale for quality of life.

Results Total 91 patients completed treatment out of which 61 patients were in vaccine group and 30 were in control group. 8.1% (5) patients in vaccine group compared to 3.33% (1) in control group found complete response for tumor regression. While partial response was found in 85% (52) patients in vaccine group compared to 93.3% (28) in control group. Administration of vaccine was associated with significantly lower side effect profile in Mw vaccine. Hematological side effects were seen in 14.4% (9) Vs 33.33% (3), gastrointestinal side effects were seen in 4.19% (3) Vs 66.66% (4) patients of vaccine and control group respectively. Skin reactions grade II were 16.4% (14) Vs 50% (15) with grade III reaction was found in 16.66% (5) patients of control group only. Mucositis grade II was seen in 21.3% (13) Vs 46.6% (14) with grade III in 16.7% (5) patients of control group only. Improvement in quality of life was found (Karnofsky performance Scale more by a mean of 10) in vaccine group. Side effects in the form of small local abscess at site of Injection only 15% cases. **Conclusion** Immunotherapy may be useful as an Adjuvant therapy in Head & Neck cancer patients receiving Chemo Radiotherapy for better clinical response, reducing side effects and improve quality of life.

Also, copies of certain other abstracts, posters and articles are filed herewith as follows:

1. Poly TLR agonist polyantigenic vaccine Cadi-05 in advanced bladder cancer.

This is a "poster" done at the AACR Annual Meeting in Washington, D.C., (April 1-5, 2006) by Dr. Khamar. It shows some of the results for the present invention. The pharmaceutical composition is cited as Cadi-05. The results are indicative of favorable response to such therapy.

2. Role of Cadi-05 as an adjuvant therapy in advanced non small cell lung cancer.

This is an abstract by several doctors/co-authors from several universities/hospitals and Dr. B. Chakrabarty of Cadila. It describes a study showing favorable results for use of Cadi-05 as an adjuvant along with chemotherapy agents (Cisplatin Plus Etoposide) enabling improved tolerance of the chemotherapy.

3. Role of Mycobacterium w as an adjuvant treatment of lung cancer(Non-small cell lung cancer).

   There is an article from the Journal of the Indian Medical Association (JIMA), Vol. 101 No. 2 (February 2003) by Sur et al., showing efficacy of the present invention per se (the tested pharmaceutical composition containing *Mycobacterium w* referred to by its trademark, Immuvac, was obtained from Cadila) and as a beneficial adjuvant to radiotherapy. Dr. Bhattachrya from Cadila provided constant help and guidance in designing and conducting this study.

4. Role of adjuvant Immunomodulator along with radiation therapy in head and Neck Cancer: A randomized trial.

   This is an article from the Journal of Clinical Radiotherapy Oncology (JCRO) Vol. 4 No. 3, pages 30-34 (September 2004) by Dr. C. Dasqupta et al., also showing significant benefit for the usage of adjuvant *Mycobacterium w* enhancing radiation tolerance, reducing radiation toxicity and improving performance status and quality of life.

With due respect, Applicants submit that one must take care to avoid conflating patent law standards of written description, utility and enablement. Written description and utility are fully satisfied in this case. The enablement requirement is limited to enabling those skilled in the art to practice the invention without undue experimentation. As stated in R.L. Harmon, "PATENTS AND THE FEDERAL CIRCUIT," 9th edition (BNA Books 2009), page 267.

> "...the specification need not necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps and interpolate between embodiments, and perhaps even extrapolate beyond and the disclosed embodiments depending upon the predictability of the art [footnote cite omitted]..."

See also, *John Hopkins University V. Cellpro*, 152 F. 3rd 1342, 47 USPQ 2d 1705 (Fed. Cir. 1995) (summary Judgment of enablement affirmed) 47 USPQ 2d 1717-19) and other screened publications.

The present application, as filed, has disclosure of how to make and use the invention so as to enable those skilled in the art to practice the invention, within the scope of each claim, subject to normal skills in the relevant art, without undue experimentation. Any of the alternatives of composition stated specifically or by limited category can be used with any of the methods of administration stated with expectation of obtaining benefit for cancer patients. It can

be done as a mono therapy or in conjunction with other therapies without undermining such other therapies or being undermined thereby. The level of disclosure in this application is consistent with many other patents and other screened publications for inventions in comparable circumstances, the experimentation on typically used implementing those therapies is not undue and the above cited and/or quoted materials show enablement in this case.

For example, typically cancer drugs are given in a dose which is effective and well tolerated. The frequency of administration is dependent on time taken for recovery from the non desired effects of a drug to minimize adverse effects of the drug. This depends on amount of drug used also. E.g. Paclitaxel is administered every three weeks when high dose is used but it is administered every week when low dose is used. In case of the present invention there is no toxicity seen at the dose administered. This provides ability to administer at higher dose levels and more frequently. The present specification provides the range for the dose and frequencies of a drug which are safe and effective. As long as one uses normal clinical acumen in selecting the dose and frequency the beneficial effect will be obtained. Efficacy rate of drugs for cancer are low compared to other drugs like antibiotics, antihypertensive, anti- diabetics etc. For this reason response to therapy is evaluated after two or three cycles and depending on the response seen the therapy is altered, e.g. change of drug in case of no response, lowering of dose in case of severe adverse event with reduction in tumor burden, increasing the dose if there is no adverse effect and poor response. This is not considered undue experimentation.

Applicants also call attention to the following book and the table extract below:

"Holland-Frei Cancer Medicine, 6th edition"

Edited by Donald W Kufe, MD,[1] Raphael E Pollock, MD, PhD,[2] Ralph R Weichselbaum, MD,[3] Robert C Bast, Jr, MD,[4] Ted S Gansler, MD, MBA,[5] James F Holland, MD, ScD (hc),[6] and Emil Frei, III, MD[1]

1Dana-Farber Cancer Institute, Harvard Medical School Boston, Massachusetts

2Department of Surgical Oncology, University of Texas, MD Anderson Cancer Center, Houston, Texas

3Department of Radiation and Cellular Oncology, University of Chicago Hospital, Chicago Tumor Institute, University of Chicago Chicago, Illinois

4University of Texas, MD Anderson Cancer Center, Houston, Texas

5American Cancer Society, Atlanta, Georgia

6Derald H Ruttenberg Cancer Center, Mount Sinai School of Medicine New York, New York

Hamilton (ON): **BC Decker**; 2003."

This book is freely available on "Pubmed" "BookShelf". This is a database maintained by US National Library of Medicine: National Institute of Health.

Please find the link below.

http://www.ncbi.nlm.nih.gov/books

The following is reproduced from Table 53-2 of Chapter 53 of the book.

	Paclitaxel	**Docetaxel**
Standard adult dose range		
(mg/m^2 q 3 wk)	135 (24-h infusion)	75–100 (1-h infusion)
	175–225 (3-h infusion)	
(mg/m^2/wk)	80	30–36

It provides for doses of Paclitaxel ranging from 80 mg/m^2 to 225 mg/m^2. 80 mg/m^2 to be given at the interval of one week while 135-225 mg/m^2 are given at the interval of three weeks. Similarly, doses of Docetaxel ranging from 30-36 mg/m^2 to 75-100 mg/m^2 30-36 mg/m^2 are given at the interval of one week and 75-100 mg/m^2 is given at the interval of three weeks.

For further examples, see the enclosed 2001 report by Clegg et al., "A rapid and systematic review of the clinical effectiveness and cost effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer. Review of the clinical effectiveness and cost effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer," Southampton Health Technology Assessment 2001: Vol. 5, No. 32 (published May 2002) showing, essentially contemporaneous with the present application filing, a high level of skill of the art, and standard rigorous methodology as part of implementation of cancer therapies developments.[1]

Note the following from page 56 of this reference at the end of its Chapter 4.

[1] Copy filed herewith.

"Trial protocols versus clinical practice
In clinical trials, patients are randomized to different therapies, and the protocol encourages adherence to therapy to the limits of tolerance, though because of side-effects, many patients do not receive complete courses. However, in routine care, two factors may affect doses and costs. Firstly, clinicians will review continuation more critically, depending on objective response (e.g. radiological evidence of tumor shrinkage) and effect on symptoms, and treatment is probably stopped earlier than in trials in those patients who do not respond. Secondly, trials usually give mean or median benefits such as survival, and this may conceal the fact that only a minority of patients benefit (perhaps 20% have survival gains, and another 20% experience symptom relief)."

See also the article, Fizazi et al., "Is 'one cycle every three or four weeks' obsolete? A critical review of dose-dense chemotherapy in solid neoplasms, ANNALS OF ONCOLOGY 11: 133-149. 2000. [Copy provided herewith].

Chemotherapy is used in a wide spectrum of neoplasms. Historically, the treatment schedule and timing of chemotherapy was dictated by neutrophil recovery kinetics. With most myelosuppressive agents used alone or in combination, peripheral granulocyte nadirs are reached in about 10-15 days and recovery is achieved in about 21 days [1]. Except in the case of nitrosoureas, these data have since been extensively substantiated. Bone marrow stem-cell proliferation is at a maximum when the granulocyte nadir is reached and recycling of chemotherapy at that point, and particularly of cycle-specific agents, may lead to considerable hematopoietic damage. It was decided that treatment intervals should be prolonged and, since the 1960s, it has been a rule of thumb to design most chemotherapy combinations to be repeated every three or four weeks. This applies to the best-known regimens such as MOPP, CHOP, CMF, FAC and PVB. The interval was often fixed in weeks and not in days, for practical reasons. It has also been shown that the speculation with action of effective radiation treatment as the sole beneficial therapy, when it is used in combination with Mycobacterium w, is not well founded.

The above paragraph indicates the role of toxicity in determining the cycle time. The article also shows that dense dose regimen is feasible and may be useful in improving survival. See abstract paragraph from the article:

Results: Dose-dense regimens were widely found to be feasible. In small-cell lung cancer, survival of patients receiving dose-dense regimens was better than that of patients treated by standard chemotherapy in three trials, two of which reached significance, when these intensive regimens allowed better dose intensity.

In view of the amendments presented and the foregoing remarks and accompanying declaration and referenced material cited above, Applicants believe that the present application is

now in compliance with 37 C.F.R. §1.112 and all other patentability requirements. Therefore, Applicants respectfully request a favorable action allowing claims 37-44, 47 and 52-72.

The cover page hereof shows payment of the extension fee and no other fees are believed necessary. However, the Director of The Patents and Trademarks Office is authorized to charge any deficiencies, or to credit any overpayments, to Deposit Account No. 03-2410; Attorney Docket No.: 81094-00004.

If any further submission by Applicants herein or their response to any questions would be helpful to the Examiner a telephone conference is encouraged.

The following information is presented in the event that a call may be deemed desirable by the Examiner:

JERRY COHEN (617) 345-3276.

Respectfully submitted,
Bakulesh M. Khamar et al, Applicants

Dated: August 17, 2010

/Jerry Cohen/
Jerry Cohen, Reg. No.: 20,522
Attorney for Applicants